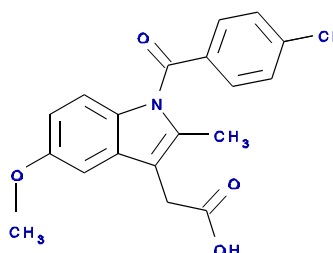


INDOMETHACIN CAPSULES, USP

DESCRIPTION:

Indomethacin cannot be considered a simple analgesic and should not be used in conditions other than those recommended under INDICATIONS AND USAGE.

Indomethacin is a nonsteroidal, anti-inflammatory, indole derivative designated chemically as 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1 *H*-indole-3-acetic acid. Indomethacin is practically insoluble in water and sparingly soluble in alcohol. It has a pKa of 4.5 and is stable in neutral or slightly acidic media and decomposes in strong alkali. The structural formula is:



M.W. 357.79

C₁₉H₁₆ClNO₄

Each capsule, for oral administration, contains ____mg of indomethacin. In addition, each capsule contains the following inactive ingredients:

(NOTE: We note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance). We believe this is an important public health measure. Please respond accordingly by correctly noting the inactive ingredients present in this product.)

CLINICAL PHARMACOLOGY:

Indomethacin is a nonsteroidal drug with anti-inflammatory, antipyretic and analgesic properties. Its mode of action, like that of other anti-inflammatory drugs, is not known. However, its therapeutic action is not due to pituitary-adrenal stimulation.

Indomethacin is a potent inhibitor of prostaglandin synthesis *in vitro*. Concentrations are reached during therapy which have been demonstrated to have an effect *in vivo* as well. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Moreover, prostaglandins are known to be among the mediators of inflammation. Since indomethacin is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

Indomethacin has been shown to be an effective anti-inflammatory agent, appropriate for long-term use in rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.

INDOMETHACIN CAPSULES, USP

Labeling Guidance
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Indomethacin affords relief of symptoms; it does not alter the progressive course of the underlying disease.

Indomethacin suppresses inflammation in rheumatoid arthritis as demonstrated by relief of pain, and reduction of fever, swelling and tenderness. Improvement in patients treated with indomethacin for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, average number of joints involved, and morning stiffness; by increased mobility as demonstrated by a decrease in walking time; and by improved functional capability as demonstrated by an increase in grip strength.

Indomethacin has been reported to diminish basal and CO₂ stimulated cerebral blood flow in healthy volunteers following acute oral and intravenous administration. In one study, after one week of treatment with orally administered indomethacin, this effect on basal cerebral blood flow had disappeared. The clinical significance of this effect has not been established.

Indomethacin capsules have been found effective in relieving the pain, reducing the fever, swelling, redness, and tenderness of acute gouty arthritis.

Following a single oral dose of indomethacin, the drug is readily absorbed, attaining peak plasma concentrations at about 2 hours. Orally administered indomethacin capsules are virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours.

Indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. The mean half-life of indomethacin is estimated to be about 4.5 hours. With a typical therapeutic regimen of 25 or 50 mg t.i.d., the steady state plasma concentrations of indomethacin are an average 1.4 times those following the first dose.

Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyl-desbenzoyl metabolites, all in the unconjugated form. About 60 percent of an oral dosage is recovered in urine as drug and metabolites (26 percent as indomethacin and its glucuronide), and 33 percent is recovered in feces (1.5 percent as indomethacin).

About 99% of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentrations. Indomethacin has been found to cross the blood brain barrier and the placenta.

INDICATIONS AND USAGE:

Indomethacin capsules have been found effective in active stages of the following:

1. Moderate to severe rheumatoid arthritis including acute flares of chronic disease.
2. Moderate to severe ankylosing spondylitis.
3. Moderate to severe osteoarthritis.
4. Acute painful shoulder (bursitis and/or tendinitis).
5. Acute gouty arthritis.

Indomethacin may enable the reduction of steroid dosage in patients receiving steroids for the more severe forms of rheumatoid arthritis. In such instances the steroid dosage should be reduced slowly and the patients followed very

closely for any possible adverse effects.

The use of indomethacin in conjunction with aspirin or other salicylates is not recommended. Controlled clinical studies have shown that the combined use of indomethacin and aspirin does not produce any greater therapeutic effect than the use of indomethacin alone. Furthermore, in one of these clinical studies, the incidence of gastrointestinal side effects was significantly increased with combined therapy (see Drug Interactions).

CONTRAINDICATIONS:

Indomethacin should not be used in:

- Patients who are hypersensitive to this product.
- Patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by aspirin or other nonsteroidal anti-inflammatory agents.

WARNINGS:

General:

Because of the variability of the potential of indomethacin to cause adverse reactions in the individual patient, the following are strongly recommended:

1. The lowest possible effective dose for the individual patient should be prescribed. Increased dosage tends to increase adverse effects, particularly in doses over 150-200 mg/day, without corresponding increases in clinical benefits.
2. Careful instructions to, and observations of, the individual patient are essential to the prevention of serious adverse reactions. As advancing years appear to increase the possibility of adverse reactions, indomethacin should be used with greater care in the aged.
3. Effectiveness of indomethacin in children has not been established. Indomethacin should not be prescribed for children 14 years of age and younger unless toxicity or lack of efficacy associated with other drugs warrants the risk.

In experience with more than 900 children reported in the literature or elsewhere who were treated with indomethacin capsules, side effects in children were comparable to those reported in adults. Experience in children has been confined to the use of indomethacin capsules.

If a decision is made to use indomethacin for children two years of age or older, such patients should be monitored closely and periodic assessment of liver function is recommended. There have been cases of hepatotoxicity reported in children with juvenile rheumatoid arthritis, including fatalities.

If indomethacin treatment is instituted, a suggested starting dose is 2 mg/kg/day given in divided doses. Maximum daily dosage should not exceed 4 mg/kg/day or 150-200 mg/day, whichever is less. As symptoms subside, the total daily dosage should be reduced to the lowest level required to control symptoms, or the drug should be discontinued.

Gastrointestinal Effects:

Single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestine, have been reported to occur with indomethacin. Fatalities have been reported in some instances.

Rarely, intestinal ulceration has been associated with stenosis and obstruction.

Gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.) have occurred. Increased abdominal pain in ulcerative colitis patients or the development of ulcerative colitis and regional ileitis have been reported to occur rarely.

Because of the occurrence, and at times severity, of gastrointestinal reactions to indomethacin, the prescribing physician must be continuously alert for any sign or symptom signaling a possible gastrointestinal reaction. The risks of continuing therapy with indomethacin in the face of such symptoms must be weighed against the possible benefits to the individual patient.

Indomethacin should not be given to patients with active gastrointestinal lesions or with a history of recurrent gastrointestinal lesions except under circumstances which warrant the very high risk and where patients can be monitored very closely.

The gastrointestinal effects may be reduced by giving indomethacin capsules immediately after meals, with food, or with antacids.

Risk of GI Ulcerations, Bleeding and Perforation with NSAID Therapy

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

Renal Effects:

As with other nonsteroidal anti-inflammatory drugs, long term administration of indomethacin to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute

interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal and renal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with conditions such as renal or hepatic dysfunction, diabetes mellitus, advanced age, extracellular volume depletion from any cause, congestive heart failure, septicemia, pyelonephritis, or concomitant use of any nephrotoxic drug. Indomethacin or other NSAIDs should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Increases in serum potassium concentration, including hyperkalemia, have been reported, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state (see PRECAUTIONS, Drug Interactions).

Since indomethacin is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; a lower daily dosage should be anticipated to avoid excessive drug accumulation.

Ocular Effects:

Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who had received prolonged therapy with indomethacin. The prescribing physician should be alert to the possible association between the changes noted and indomethacin. It is advisable to discontinue therapy if such changes are observed. Blurred vision may be a significant symptom and warrants a thorough ophthalmological examination. Since these changes may be asymptomatic, ophthalmologic examination at periodic intervals is desirable in patients where therapy is prolonged.

Central Nervous System Effects:

Indomethacin may aggravate depression or other psychiatric disturbances, epilepsy, and parkinsonism, and should be used with considerable caution in patients with these conditions. If severe CNS adverse reactions develop, indomethacin should be discontinued.

Indomethacin may cause drowsiness; therefore, patients should be cautioned about engaging in activities requiring mental alertness and motor coordination, such as driving a car. Indomethacin may also cause headache. Headache which persists despite dosage reduction requires cessation of therapy with indomethacin.

Use in Pregnancy and the Neonatal Period:

Indomethacin is not recommended for use in pregnant women, since safety for use has not been established, and because of the known effect of drugs of this class on the human fetus (closure of the ductus arteriosus, platelet dysfunction with resultant bleeding, renal dysfunction or failure with

oligohydramnios, gastrointestinal bleeding or perforation, and myocardial degenerative changes) during the third trimester of pregnancy.

Teratogenic studies were conducted in mice and rats at dosages of 0.5, 1, 2, and 4 mg/kg/day. Except for retarded fetal ossification at 4 mg/kg/day considered secondary to the decreased average fetal weights, no increase in fetal malformations was observed as compared with control groups. Other studies in mice reported in the literature using higher doses (5 to 15 mg/kg/day) have described maternal toxicity and death, increased fetal resorptions, and fetal malformations. Comparable studies in rodents using high doses of aspirin have shown similar maternal and fetal effects.

As with other nonsteroidal anti-inflammatory agents which inhibit prostaglandin synthesis, indomethacin has been found to delay parturition in rats.

In rats and mice, 4 mg/kg/day given during the last three days of gestation caused a decrease in maternal weight gain and some maternal and fetal deaths. An increased incidence of neuronal necrosis in the diencephalon in the live-born fetuses was observed. At 2 mg/kg/day, no increase in neuronal necrosis was observed as compared to the control groups. Administration of 0.5 or 4 mg/kg/day during the first three days of life did not cause an increase in neuronal necrosis at either dose level.

Use in Nursing Mothers:

Indomethacin is excreted in the milk of lactating mothers. Indomethacin is not recommended for use in nursing mothers.

PRECAUTIONS:

General

Nonsteroidal anti-inflammatory drugs, including indomethacin may mask the usual signs and symptoms of infection. Therefore, the physician must be continually on the alert for this and should use the drug with extra care in the presence of existing controlled infection.

Fluid retention and peripheral edema have been observed in some patients taking indomethacin. Therefore, as with other nonsteroidal anti-inflammatory drugs, indomethacin should be used with caution in patients with cardiac dysfunction, hypertension, or other conditions predisposing to fluid retention.

In a study of patients with severe heart failure and hyponatremia, indomethacin was associated with significant deterioration of circulatory hemodynamics, presumably due to inhibition of prostaglandin dependent compensatory mechanisms.

Indomethacin, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation. This effect is of shorter duration than that seen with aspirin and usually disappears within 24 hours after discontinuation of indomethacin. Indomethacin has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this effect may be exaggerated in patients with underlying hemostatic defects, indomethacin

should be used with caution in persons with coagulation defects.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with indomethacin. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with indomethacin as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), indomethacin should be discontinued.

Information for Patients:

Indomethacin, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs (Nonsteroidal Anti-inflammatory Drugs) are often essential agents in the management of arthritis; but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and the physician.

Laboratory Tests

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see WARNINGS, Risk of GI Ulcerations, Bleeding and Perforation with NSAID Therapy).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In an 81-week chronic oral toxicity study in the rat at doses up to 1 mg/kg/day, indomethacin had no tumorigenic effect.

Indomethacin produced no neoplastic or hyperplastic changes related to treatment in carcinogenic studies in the rat (dosing period 73-110 weeks) and the mouse (dosing period 62-88 weeks) at doses up to 1.5 mg/kg/day.

Indomethacin did not have any mutagenic effect in *in vitro* bacterial tests (Ames test and *E. Coli* with or without metabolic activation) and a series of *in vivo* tests including the host-mediated assay, sex-linked recessive lethals

in *Drosophila*, and the micronucleus test in mice.

Indomethacin at dosage levels up to 0.5 mg/kg/day had no effect on fertility in mice in a two generation reproduction study or a two litter reproduction study in rats.

Drug Interactions:

In normal volunteers receiving indomethacin, the administration of diflunisal decreased the renal clearance and significantly increased the plasma levels of indomethacin. In some patients, combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage. Therefore, diflunisal and indomethacin should not be used concomitantly.

In a study in normal volunteers, it was found that chronic concurrent administration of 3.6 g of aspirin per day decreases indomethacin blood levels approximately 20%.

Clinical studies have shown that indomethacin does not influence the hypoprothrombinemia produced by anticoagulants. However, when any additional drug, including indomethacin, is added to the treatment of patients on anticoagulant therapy, the patients should be observed for alterations of the prothrombin time.

When indomethacin is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased. Therefore, a lower total daily dosage of indomethacin may produce a satisfactory therapeutic effect. When increases in the dose of indomethacin are made, they should be made carefully and in small increments.

Caution should be used if indomethacin is administered simultaneously with methotrexate. Indomethacin has been reported to decrease the tubular secretion of methotrexate and to potentiate its toxicity.

Administration of nonsteroidal anti-inflammatory drugs concomitantly with cyclosporine has been associated with an increase in cyclosporine-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking cyclosporine, and renal function should be carefully monitored.

Indomethacin capsules 50 mg t.i.d. produced a clinically relevant elevation of plasma lithium and reduction in renal lithium clearance in psychiatric patients and normal subjects with steady state plasma lithium concentrations. This effect has been attributed to inhibition of prostaglandin synthesis. As a consequence, when indomethacin and lithium are given concomitantly, the patient should be carefully observed for signs of lithium toxicity. (Read circulars for lithium preparations before use of such concomitant therapy.) In addition, the frequency of monitoring serum lithium concentration should be increased at the outset of such combination drug treatment.

In some patients, the administration of indomethacin can reduce the diuretic, natriuretic, and, antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when indomethacin and diuretics are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Indomethacin reduces basal plasma renin activity (PRA), as well as those elevations of PRA induced by furosemide administration, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients.

It has been reported that the addition of triamterene to a maintenance schedule of indomethacin resulted in reversible acute renal failure in two of four healthy volunteers. Indomethacin and triamterene should not be administered together.

Indomethacin and potassium-sparing diuretics each may be associated with increased serum potassium levels. The potential effects of indomethacin and potassium-sparing diuretics on potassium kinetics and renal function should be considered when these agents are administered concurrently.

Most of the above effects concerning diuretics have been attributed, at least in part, to mechanisms involving inhibition of prostaglandin synthesis by indomethacin.

Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by nonsteroidal anti-inflammatory drugs including indomethacin has been reported. Therefore, when using these blocking agents to treat hypertension, patients should be observed carefully in order to confirm that the desired therapeutic effect has been obtained. There are reports that indomethacin can reduce the antihypertensive effect of captopril in some patients.

False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

Pediatric Use:

Effectiveness in pediatric patients 14 years of age and younger has not been established (see WARNINGS).

ADVERSE REACTIONS:

The adverse reactions for indomethacin capsules listed in the following table have been arranged in two groups: (1) incidence greater than 1% and (2) incidence less than 1%. The incidence for group (1) was obtained from 33 double-blind controlled clinical trials reported in the literature (1,092 patients). The incidence for group (2) was based on reports in clinical trials, in the literature, and on voluntary reports since marketing. The probability of a causal relationship exists between indomethacin and these adverse reactions, some of which have been reported only rarely.

Incidence greater
than 1%

Incidence less than 1%

GASTROINTESTINAL

nausea* with or without vomiting	anorexia	gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.)
dyspepsia* (including indigestion, heartburn and epigastric pain)	bloating (includes distention)	development of ulcerative colitis and regional ileitis
diarrhea	flatulence	ulcerative stomatitis
abdominal distress or pain	peptic ulcer	toxic hepatitis and jaundice (some fatal cases have been reported)
constipation	gastroenteritis	
	rectal bleeding	
	proctitis	
	single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestines	
	intestinal ulceration associated with stenosis	

and obstruction

Incidence greater
than 1%

Incidence less than 1%

CENTRAL NERVOUS SYSTEM

headache(11.7%)

dizziness*

vertigo

somnolence

depression and fatigue
(including malaise and
listlessness)anxiety (includes
nervousness)

muscle weakness

involuntary muscle
movement

insomnia

muzziness

psychic disturbances
including psychotic
episodes

mental confusion

drowsiness

light-headedness

syncope

paresthesia

aggravation of epilepsy
and parkinsonism

depersonalization

coma

peripheral neuropathy

convulsions

dysarthria

SPECIAL SENSES

tinnitus

ocular - corneal
deposits and retinal
disturbances,
including those of
the macula, have
been reported in
some patients on
prolonged therapy
with indomethacin

blurred vision

diplopia,

hearing disturbances,

deafness

CARDIOVASCULAR

none

hypertension

hypotension

tachycardia

chest pain

congestive heart failure

arrhythmia; palpitations

METABOLIC

none

edema

weight gain

fluid retention

flushing or sweating

hyperglycemia

glycosuria

hyperkalemia

INTEGUMENTARY

none

pruritus

rash; urticaria

petechiae or ecchymosis

exfoliative dermatitis

erythema nodosum

loss of hair

Stevens-Johnson

syndrome

erythema multiforme

toxic epidermal

Indomethacin Capsules, USP

Labeling Guidance
Revised September, 1995

necrolysis

Incidence greater
than 1%

Incidence less than 1%

HEMATOLOGIC

none

leukopenia
bone marrow depression
anemia secondary to
obvious or occult
gastrointestinal
bleedingaplastic anemia
hemolytic anemia
agranulocytosis
thrombocytopenic purpura
disseminated intravas-
cular coagulation

HYPERSENSITIVITY

none

acute anaphylaxis
acute respiratory distress
rapid fall in blood pressure
resembling a shock-like
state
angioedemadyspnea
asthma
purpura
angiitis
pulmonary edema
fever

GENITOURINARY

none

hematuria
vaginal bleeding
proteinuria
nephrotic syndrome
interstitial nephritisBUN elevation
renal insufficiency
including renal
failure

MISCELLANEOUS

none

epistaxis
breast changes,
including enlargement
and tenderness, or
gynecomastia

*Reactions occurring in 3% to 9% of patients treated with indomethacin.
(Those reactions occurring in less than 3% of the patients are unmarked).

Causal relationship unknown: Other reactions have been reported but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, the possibility cannot be excluded. Therefore, these observations are being listed to serve as alerting information to physicians:

Cardiovascular: Thrombophlebitis.

Hematologic: Although there have been several reports of leukemia, the supporting information is weak.

Genitourinary: Urinary frequency.

A rare occurrence of fulminant necrotizing fasciitis, particularly in association with Group A β -hemolytic streptococcus, has been described in

persons, treated with nonsteroidal anti-inflammatory agents, including indomethacin, sometimes with fatal outcome (see PRECAUTIONS, General).

OVERDOSAGE:

The following symptoms may be observed following overdosage: nausea, vomiting, intense headache, dizziness, mental confusion, disorientation, or lethargy. There have been reports of paresthesias, numbness, and convulsions.

Treatment is symptomatic and supportive. The stomach should be emptied as quickly as possible if the ingestion is recent. If vomiting has not occurred spontaneously, the patient should be induced to vomit with syrup of ipecac. If the patient is unable to vomit, gastric lavage should be performed. Once the stomach has been emptied, 25 to 50 g of activated charcoal may be given. Depending on the condition of the patient, close medical observation and nursing care may be required. The patient should be followed for several days because gastrointestinal ulceration and hemorrhage have been reported as adverse reactions of indomethacin. Use of antacids may be helpful.

The oral LD₅₀ of indomethacin in mice and rats (based on 14 day mortality response) was 50 and 12 mg/kg, respectively.

DOSAGE AND ADMINISTRATION:

Adverse reactions appear to correlate with the size of the dose of indomethacin in most patients but not all. Therefore, every effort should be made to determine the smallest effective dosage for the individual patient.

Always give indomethacin capsules with food, immediately after meals, or with antacids to reduce gastric irritation.

Pediatric Use:

Indomethacin ordinarily should not be prescribed for pediatric patients 14 years of age and under (see WARNINGS).

Adult Use

Dosage Recommendations for Active Stages of the Following:

1. Moderate to severe rheumatoid arthritis including acute flares of chronic disease; moderate to severe ankylosing spondylitis; and moderate to severe osteoarthritis.

Suggested Dosage:

Indomethacin capsules 25 mg b.i.d. or t.i.d. If this is well tolerated, increase the daily dosage by 25 or by 50 mg, if required by continuing symptoms, at weekly intervals until a satisfactory response is obtained or until a total daily dose of 150-200 mg is reached. DOSES ABOVE THIS AMOUNT GENERALLY DO NOT INCREASE THE EFFECTIVENESS OF THE DRUG.

In patients who have persistent night pain and/or morning stiffness, the giving of a large portion, up to a maximum of 100 mg, of the total daily dose at bedtime, may be helpful in affording relief. The total daily dose should not exceed 200 mg. In acute flares of chronic rheumatoid arthritis, it may be necessary to increase the dosage by 25 mg or, if required, by 50 mg daily.

If minor adverse effects develop as the dosage is increased, reduce the dosage rapidly to a tolerated dose and OBSERVE THE PATIENT CLOSELY.

If severe adverse reactions occur, STOP THE DRUG. After the acute phase of the disease is under control, an attempt to reduce the daily dose should be made repeatedly until the patient is receiving the smallest effective dose or the drug is discontinued.

Careful instructions to, and observations of, the individual patient are essential to the prevention of serious, irreversible, including fatal, adverse reactions.

As advancing years appear to increase the possibility of adverse reactions, indomethacin should be used with greater care in the aged.

2. Acute painful shoulder (bursitis and/or tendinitis).

Initial Dose:

75-150 mg daily in 3 or 4 divided doses.

The drug should be discontinued after the signs and symptoms of inflammation have been controlled for several days. The usual course of therapy is 7-14 days.

3. Acute gouty arthritis.

Suggested Dosage:

Indomethacin capsules 50 mg t.i.d. until pain is tolerable. The dose should then be rapidly reduced to complete cessation of the drug. Definite relief of pain has been reported within 2 to 4 hours. Tenderness and heat usually subside in 24 to 36 hours, and swelling gradually disappears in 3 to 5 days.

HOW SUPPLIED

- Established name
- Strength, dosage form
- Packaging
- Shape, color, imprinting or other identifying characteristics
- NDC Number
- Special handling and storage conditions
- Dispensing Statement
- CAUTION: Federal law...

(Rev. Date _____)

Manufactured By Statement

Indometh.cap

Indomethacin Capsules, USP

Labeling Guidance
Revised September, 1995

9/27/95